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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/248,178	02/09/1999	STEVEN G. REED	210121.446C2	8493

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EXAMINER	
SHEINBERG, MONIKA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/06/2002 LY

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/248,178	Applicant(s) REED ET AL.	
	Examiner Monika B Sheinberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-52 and 107-124* is/are pending in the application.

4a) Of the above claim(s) *45-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *107-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *45-52 and 107-124* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment F

Applicants' arguments, filed 12 August 2002, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restriction

Claims 45-52 and 107-124 are pending.

No amendment is present in the instant application that cancels the indicated withdrawn claims. Applicants are reminded that claims 45-52 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as recited in the office action mailed 31 October 2000; as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12, filed: 21 September 2000.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 107-124, as necessitated amendment, are rejected under U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 107-124 all include primers and probes that either a) amplify polynucleotide sequences including the elected sequences as seen in claims 107-115; or b) or comprise the elected sequences as seen in claims 116-124. These sequences, beyond exact complementarity and lengths of the elected SEQ ID NOs, are included but not disclosed as to written description.

As written: "at least two oligonucleotide primers such that the polynucleotide sequence recited in SEQ ID NO: 55 is amplified" (claim 107, lines 4-5), claims 107-115 encompass sequences larger than the elected sequence (i.e. SEQ ID NO: 55) that still include the elected sequence, due to the lack of specificity of the oligonucleotide primers required by the claims. Thus the claims are not limited to the amplification of the elected sequences alone. As written: "an oligonucleotide probe comprising the polynucleotide sequence of SEQ ID NO: 55" (claim 116, lines 4-5), claims 116-124 encompass probes of larger sequences that include the elected sequence but are not limited to the exact sequences of SEQ ID NO: 55, 59-65, and 67. The sequences identified (by SEQ ID) per se meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 107-124 are directed to encompass DNA gene sequences, corresponding sequences from other species, mutated fragment sequences, allelic variants, splice variants, and so forth. None of these additional sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Claims 107-124, as necessitated by amendment are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPA 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The instant application fails to provide guidance to one of ordinary skill in the art for detecting the presence of breast cancer. Claims 107-115 read, for example as in claim 107, that detection of any amplified sequence by primers that have the ability to amplify SEQ ID NO: 55 will result in the detection of breast cancer upon the comparison of the amount amplified to those amplified in a normal sample. Claims 116-124 read, for example as in claim 116, that the detection of hybridized probe (SEQ ID NO: 55) to a sample will result in the detection of breast cancer upon the comparison of the amount of the same hybridized probe in normal samples. Detection or amplification alone does not provide statistically significant information. The specification provides no basis for comparison to determine what level or amount of expression is correlated to the "presence" of breast cancer. The specification offers no guidance to enable the skilled artisan to use levels or amount of amplified nucleotide sequences to determine the presence of breast cancer. Example 1 on page 32, states phrases such as "elevated expression" (line 16) or "overexpressed" (line 24) however these do not define any specified level or amount. The specification teaches that the skilled artisan must determine the amount of the sequences amplified and compare with the amount of detected in normal samples, however the specification does not teach the amount or threshold difference of sequences amplified in the biological sample that is indicative of the presence of breast cancer. In addition, the specification discloses on page 31, an example that discloses analyzed results showing over-expressed levels in the breast tumor cDNA library with low levels of expression in "all normal tissues tested" (line 27). This demonstrates that the elected sequences and their oligonucleotide primers were present to some degree in all samples. The specification does not provide evidence of a comparison with normal breast tissue. Although a breast tumor specific cDNA library was created (p. 31, line 8) from a subtraction process from breast tumor and normal breast cDNA libraries; the elected sequences appear to be partial cDNA clones from different experiments in which the specification carries out an expression analysis to "normal tissues". However, the specification does not provide normal breast tissue to be included within these tissues. Thus the elected sequences have not been shown to be overexpressed in breast tumor versus normal breast, the results of which are unpredictable, due to the lack of a comparison between the two. Due to detection in all samples, the elected sequences and their primers are not diagnostic of breast

cancer unless elevated levels of expression are observed in a comparison between tumorous and normal breast samples.

In addition, as per the applicants' disclosure of the degree of specificity required for the oligonucleotide primer "at least about 60%" (page 28, lines 21-24). The sequences of the prior art disclosed below, as oligonucleotide primers, are 100% specific at various lengths from 21 nucleotides in length and greater. The claims do not require that the biological sample be of breast tissue, thus they read upon any biological sample, including for example a hair sample. The prior art demonstrates that oligonucleotide primers of the elected sequences are detected in non-specific tissue and species; for example prostate, colon, lung, along with species such as plant, rat, swine, etc. The following are some examples: (Please see the attached packet of sequence alignment search results of commercial databases for more examples from the office action mailed: 07 May 2002).

- SEQ ID NO: 55; accession # AA003705 (22-Jul-1996), a sequence of a mouse (total fetus) has 23 contiguous nucleotides with 100% similarity.
- SEQ ID NO: 59; US Patent 6,261,562 (with *common inventors*; filed 09-Feb-1998), sequence 73 of the prostate has 325 contiguous nucleotides with 100% similarity.
- SEQ ID NO: 60; WO 9818931 (22-May-1998), a sequence of Streptococcus pneumoniae has 17 contiguous nucleotides with 100% similarity
- SEQ ID NO: 61; US Patent 6,239,264 (filed 24-Dec-1997), sequence 136 of fungi has 68 contiguous nucleotides with 100% similarity.
- SEQ ID NO: 62; US Patent 5,770,366 (filed 29-Jul-1994), a sequence of a Melanoma-inhibiting protein has 18 contiguous nucleotides with 100% similarity.
- SEQ ID NO: 63; WO 9835693 (20-Aug-1998), a sequence of a secreted protein has 21 contiguous nucleotides with 100% similarity.
- SEQ ID NO: 64; WO 9316178 (19-Aug-1993), a sequence of the brain has 27 contiguous nucleotides with 100% similarity.
- SEQ ID NO: 65; US Patent 6,210,883 (filed 18-Mar-1998), sequence 27 of the lung has 319 contiguous nucleotides with 100% similarity.

- SEQ ID NO: 67; WO 9505457 (23-Feb-1995), a sequence of Oryza sativa has 21 contiguous nucleotides with 100% similarity.

The above sequences can be used to design primers that could amplify the elected sequence in addition to other sequences. Due to the use of unspecified primer sequences, sequences, including unknown, will be detected. These sequences that are being detected can encompass non-elected sequences, due to the claims not requiring that the amount of amplified ELECTED sequence be detected or determined. Thus as discussed before, the claimed methods in are not capable of being diagnostic of breast cancer. The examples provided are only a generic description of the claimed method. In addition to the fact that no specific type of breast cancer is disclosed. Tumorous breast samples still does not indicate what kind the cancer is. It appears the methods are claiming diagnostic abilities of any and all breast cancers.

A correlation between any tissue sample and breast cancer is clearly unpredictable in light of the state of the art. It is unclear to what degree of amplification the detected amount of amplified sequence is required for the detecting of the presence of breast cancer. Without evidence as to the correlation between levels expression and the presence of breast cancer, the skilled artisan would be required to practice undo experimentation to determine the amounts of expression required to determine the presence of breast cancer in a patient. While working examples are not, per se, required, the specification must provide adequate guidance such that one of skill in the art could practice the invention without undue experimentation. Given the lack of descriptive working examples in the specification, and the unpredictability of detecting the presence of breast cancer, the specification, as filed is not enabling for the method of using the elected sequences nor the oligonucleotide primers or probes as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 107-124, as necessitated by amendment, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 107-115 are vague and indefinite due to the lack of clarity of the phrase "derived by", as seen for example in claim 107, line 10. It is unclear as to what is actually is being compared (i.e. homologues or variants) due to the derivation of a product could include more steps that indicated; the exact means by which the sequence is derived is unclear. Thus claims 107-115 are vague and indefinite.

Claims 107-115 are vague and indefinite due to the lack of clarity of the phrase "amplified polynucleotide sequence" as seen for example in claim 107, line 7. It is unclear as to whether the indicated sequences are only specific to elected sequence within the claim (i.e. SEQ ID NO: 55) or inclusive of any possible polynucleotide sequence that could be amplified by the non-specific oligonucleotide primers of the claim. Thus claims 107-115 are vague and indefinite.

Claims 116-124 are vague and indefinite due to the lack of clarity of the phrase "an oligonucleotide probe comprising the polynucleotide sequence of SEQ ID NO: 55" as seen for example in claim 116, lines 4-5. It is unclear as to whether the indicated probe sequences are specific to the elected sequences within the claim (i.e. SEQ ID NO: 55) or are inclusive of probes of larger sequences that include the elected sequence but are not limited to the exact sequences of SEQ ID NO: 55, 59-65, and 67. Thus claims 116-124 are vague and indefinite.

Claims 107-124 are indefinite for failing to recite a final process step that agrees back with the preamble. While minor details are not required in method/process claims, at least the basic steps must be recited in a positive, active fashion. For example, claim 107 is drawn to a method of detecting the present of breast cancer, yet the claim recites a final step of comparing amounts of amplified polynucleotide sequences. Claim 116 is also drawn to a method of detecting breast cancer, yet the claim recites a final step of comparing the amount of hybridized sequences to a probe. It is unclear whether the methods claimed are a method to detection or a method to compare. The claims do not set forth the conditions/state when the methods have "detected the presence of breast cancer".

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (703) 306-0511. The examiner can normally be reached on Monday-Friday from 1 P.M to 8 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

November 1, 2002

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